Kidney360

AKI in Hospitalized Patients with COVID-19 and Seasonal Influenza: A Comparative Analysis

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Key Points

- The rate of AKI is similar in COV-AKI and FLU-AKI, although risk of stage 3 AKI is higher in COV-AKI and is associated with a poorer prognosis.
- Black race and mechanical ventilation are associated with a higher risk of COV-AKI. CKD is a major risk factor for AKI in both groups.
- COV-AKI is associated with a 2.3-fold higher odds of proteinuria 2+ or more in comparison with FLU-AKI.

Abstract

Background Coronavirus disease 2019 (COVID-19) is often compared with seasonal influenza and the two diseases have similarities, including the risk of systemic manifestations such as AKI. The aim of this study was to perform a comparative analysis of the prevalence, risk factors, and outcomes of AKI in patients who were hospitalized with COVID-19 and influenza.

Methods Retrospective cohort study of patients who were hospitalized with COVID-19 (n=325) or seasonal influenza (n=433). AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Baseline characteristics and hospitalization data were collected, and multivariable analysis was performed to determine the independent predictors for AKI.

Results AKI occurred in 33% of COVID-19 hospitalizations (COV-AKI) and 33% of influenza hospitalizations (FLU-AKI). After adjusting for age, sex, and comorbidity count, the risk of stage 3 AKI was significantly higher in COV-AKI (OR, 3.46; 95% CI, 1.63 to 7.37). Pre-existing CKD was associated with a six- to seven-fold increased likelihood for FLU-AKI and COV-AKI. Mechanical ventilation was associated with a higher likelihood of developing AKI in the COVID-19 cohort (OR, 5.85; 95% CI, 2.30 to 15.63). Black race, after adjustment for comorbidities, was an independent risk for COV-AKI.

Conclusions Pre-existing CKD was a major risk factor for AKI in both cohorts. Black race (independent of comorbidities) and mechanical ventilation were associated with a higher risk of developing COV-AKI, which is characterized by a higher burden of stage 3 AKI and overall poorer prognosis.

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Introduction

Coronavirus disease 2019 (COVID-19) is a term encompassing the varied clinical manifestations caused by the novel severe acute respiratory syndrome coronavirus 2. This novel RNA virus emerged in the Wuhan province of China in 2019 and as of December 3, 2020, it has infected 64,863,145 individuals and caused 1,499,586 deaths worldwide, with 237,760 deaths in the United States alone (1). Numerous reports have clearly demonstrated that AKI is a frequent complication of COVID-19, with the incidence of AKI ranging between 8% and 68% (2–7). Kidney dysfunction in COVID-19 has been demonstrated to be an independent risk factor for mortality in patients who were hospitalized (8,9). The emerging risk factors for AKI in COVID-19 (COV-AKI) include male sex, Black race, hypertension (HTN), diabetes mellitus (DM), and congestive heart failure (CHF) (2,7). In addition to AKI, other manifestations of kidney involvement in COVID-19 include electrolyte disorders, hematuria, and proteinuria (10). Various mechanisms have been proposed for kidney involvement in COVID-19, and these include massive cytokine release, organ crosstalk, and the effect of other organ system involvement on kidney

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function (5,11). Approximately 4%–15% of patients developing COV-AKI require RRT (2,5). The surge in patients with COVID-19 across the United States resulted in a rapid rise in the need for RRT, and the subsequent shortages in dialysis machines, replacement solutions, and consumables has made hospital systems re-evaluate their RRT preparedness.

COVID-19 has been compared with seasonal influenza due to its pandemic potential and risk for severe respiratory failure (12,13). It is now clear the mortality of COVID-19 exceeds that of seasonal influenza and COVID-19 has been associated with a number of novel sequalae (14,15). AKI from varying etiologies occurs in seasonal influenza (FLU-AKI) with a reported incidence of approximately 34%–67% and RRT use of 11%–36% (16–18). Whether these two diseases share similar risk factors for AKI and need for RRT remains unknown.

This study seeks to address these questions by performing a comparative analysis focusing on prevalence, risk factors, characteristics, and complications of AKI in patients who were hospitalized with COVID-19 or seasonal influenza.

Materials and Methods

Cohort Identification

This study was approved by the Institutional Review Board at the Medical College of Wisconsin. The electronic health record (EHR) was queried to identify patients who were hospitalized with influenza or COVID-19 within the Froedtert Health system in Milwaukee, WI, using International Statistical Classification of Diseases and Related Health Problems (ICD-10-CM) codes (Supplemental Table 1). The Froedtert Health system includes a 735-bed tertiary care hospital and two community hospitals with 272 beds. The inclusion criteria were: (*1*) adults aged ≥18 years; (*2*) admission for influenza related illness between December 15, 2017 and March 20, 2018 or COVID-19–related illness between February 1, 2020 and June 30, 2020. The exclusion criteria were: (*1*) history of ESKD, (*2*) history of kidney transplantation, and (*3*) age <18 years. The EHR was reviewed by members of the investigative team to: (*1*) confirm the diagnosis of COVID-19 or seasonal influenza and inpatient admission; (*2*) confirm the diagnosis and stage of AKI according to Kidney Disease Improving Global Outcomes criteria (19); (*3*) abstract urinalysis and urine microscopy data; (*4*) identify the type and duration of RRT; and (*5*) identify patients who experience death with rising creatinine and oliguria (DWRCO) (20).

Baseline clinical characteristics abstracted from the EHR included patient demographics, residence on admission, body mass index (BMI), DM, HTN, CKD and stage of CKD, CHF, coronary artery disease (CAD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), asthma, use of renin angiotensin aldosterone system (RAAS) blocking agents (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), immunosuppressed status (HIV positive, use of mycophenolate mofetil, cyclophosphamide, or oral corticosteroids, or cancer chemotherapy), neutrophil/lymphocyte ratio, and baseline serum creatinine (sCr). Baseline sCr was determined by chart review as the most recent stable sCr value within 1 year before admission. Hospitalization characteristics that were assessed included: nephrology consultation, need for intensive care unit (ICU) admission, vasopressor and/or inotropic administration, mechanical ventilation, length of stay (LOS), and in-hospital and 30-day mortality. In those patients meeting criteria for AKI, the additional variables recorded included: stage of AKI, DWRCO, and need for, and type of, RRT.

Statistical Analyses

Descriptive statistics were conducted to summarize cohort characteristics. Chi-square and Fisher's exact test were used for comparison of categorical variables and the ANOVA test for comparison of continuous values. Comparisons were conducted first in the full cohort by virus type (COVID-19 and influenza); then by AKI status in the two cohorts; lastly in the AKI cohort by virus type (COVID-19 and influenza).

Unadjusted and adjusted logistic regression models were used to investigate patients' demographics, risk, and clinical factors, and their relationship with three outcomes of interest: (*1*) AKI, (*2*) AKI stage 3, and (*3*) urine findings. We first conducted univariate logistic models to estimate the odds of having AKI in COVID-19 and influenza cohorts separately. On the basis of the univariate analyses and clinical significance, multivariate logistic regression models for AKI and urine findings were adjusted for demographics (sex, age, ethnicity/race), comorbidity (DM, HTN, CKD, CHF, CAD), with additional variables of ICU transfer and mechanical ventilation for AKI only. The AKI stage 3 multivariate regression model was only adjusted for virus type, sex, age, and comorbidity count due to sample size limitations. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided tests were conducted, and $P<0.05$ was considered statistically significant. Data are presented as median (interquartile range; IQR) for continuous variables or number (%) for dichotomous variables.

Results

A total of 758 patients were included in this study, 325 in the COVID-19 cohort and 433 in the influenza cohort. The baseline characteristics of the study cohort are shown in Supplemental Table 2. The individuals in the COVID-19 cohort were younger (median age, 64; IQR, 50–77 years), with the majority being males (51%) and predominantly Black (51%). In contrast, the influenza group was older (median age, 72; IQR, 60–84 years) with a higher proportion of females (60%) and non-Hispanic White patients (72%). The COVID-19 cohort included more individuals (23% versus 12%, $P<0.001$) who were admitted from a long-term care facility (nursing home residents/long-term acute care units/rehabilitation homes) rather than home. The median BMI (30.5 versus 28.1 kg/m^2, $P=0.007$) and prevalence of DM were significantly higher in the COVID-19 group (44% versus 36%, $P=0.03$), whereas the prevalence of other comorbidities (HTN, CHF, CAD, PVD, COPD, asthma, and CKD) was higher in individuals admitted with influenza. Of these comorbidities, only the higher prevalence of HTN, CAD, COPD, and asthma achieved statistical significance. Individuals with COVID-19 were less likely to be immunosuppressed (12% versus 46%, $P<0.0001$) and were likely to have a lower neutrophil/lymphocyte ratio on

admission (4.3 versus 7.0, $P<0.0001$). The proportion of patients with two or more comorbidities was higher in the influenza cohort in comparison with the COVID-19 cohort (67% versus 56%, $P=0.002$). There were no statistically significant differences in PVD, CKD, stage of CKD, baseline or admission sCr, or use of RAAS medications between the two cohorts.

Hospital characteristics are presented in Supplemental Table 3. In comparison with the influenza cohort, the rates of nephrology consultation (7% versus 3%; $P=0.02$), vasopressor use (14% versus 10%, $P=0.05$), and mechanical ventilation (13% versus 7%; $P=0.002$) were significantly higher in the COVID-19 cohort. In-hospital mortality (5% versus 2%, $P=0.005$) and 30-day mortality (12% versus 6%, $P=0.004$) were higher in the COVID-19 cohort in comparison with the influenza cohort, as was the median LOS (6; IQR, 3–12 days versus 4; IQR, 2–6 days, $P<0.0001$). The rate of ICU admission or inotrope use did not significantly differ between the two groups.

A comparison of the baseline characteristics of the AKI and non-AKI groups in both cohorts is shown in Table 1. A total of 106 patients with COVID-19 developed AKI (COV-AKI), whereas 143 patients developed AKI in the influenza cohort (FLU-AKI). The patients with COV-AKI were older (median age, 67; IQR, 57–81 years), predominantly Black (64%), and had a higher prevalence of DM (58%), HTN (63%), CAD (27%), CHF (37%), and CKD (54%) in comparison with patients with COVID-19 without AKI (COV-NoAKI). Most of the patients with COV-AKI had Medicare insurance (72%) and 37% of patients with COV-AKI had a comorbidity count of four or more. The baseline sCr was significantly higher in the COV-AKI group and this group had a higher rate of RAAS medication use than the COV-NoAKI cohort. The remaining variables (sex, BMI, PVD, asthma, COPD, immunosuppression) were not statistically different between the COV-AKI and COV-NoAKI subsets. A comparison of FLU-AKI and FLU-NoAKI groups showed the predominant race in FLU-AKI subset was non-Hispanic White, and this group was more likely to have underlying CKD, CHF, and a higher comorbidity count (four or more) than the FLU-NoAKI group. As with COV-AKI, the subjects in the FLU-AKI cohort also had a higher baseline sCr in comparison with the FLU-NoAKI subset.

The characteristics of COV-AKI and FLU-AKI are shown in Figure 1. The COV-AKI group had a higher admission sCr (1.6 mg/dl, IQR, 1.2–2.2 versus 1.4 mg/dl; IQR, 1.1–1.9, $P=0.04$) whereas the baseline and discharge sCr were similar, although not statistically significant, between the two

Table 1. Baseline characteristics by AKI status in the study cohorts

Clinical Variable	Coronavirus Disease 2019			Influenza		
	No AKI ($n=219$)	AKI ($n=106$)	P value	No AKI ($n=290$)	AKI ($n=143$)	P value
Age (yr)	62 (47–75)	67 (57–81)	0.01	72 (59–85)	73 (60–84)	0.5
Female	111 (51)	47 (44)	0.3	180 (62)	81 (57)	0.3
Race			0.006			0.02
Black	99 (45)	68 (64)		58 (20)	46 (32)	
Non-Hispanic white	86 (39)	28 (26)		221 (76)	92 (64)	
Hispanic/other	34 (16)	10 (9)		11 (4)	5 (4)	
Primary payor			<0.0001			0.09
Medicare	110 (50)	76 (72)		215 (74)	116 (81)	
Medicaid	38 (17)	13 (12)		32 (11)	17 (12)	
Managed care	71 (32)	15 (14)		41 (14)	9 (6)	
Other	0	2 (2)		2 (0.7)	1 (0.7)	
BMI, kg/m^2	31.2 (26.3–36.1)	28.6 (24.4–37.1)	0.99	27.9 (23.9–33.8)	29.6 (24.7–34.9)	0.2
Residence on admit			0.03			0.07
Home	177 (81)	74 (70)		261 (90)	120 (84)	
Other	42 (19)	32 (30)		29 (10)	23 (16)	
Diabetes mellitus	71 (37)	56 (58)	0.0005	87 (33)	56 (42)	0.07
Hypertension	96 (50)	60 (63)	0.04	165 (62)	93 (69)	0.1
Heart failure	34 (18)	35 (37)	0.0004	60 (22)	52 (39)	0.0005
CAD	31 (16)	26 (27)	0.03	76 (28)	41 (31)	0.6
PVD	14 (7)	8 (8)	0.7	30 (11)	15 (11)	1
COPD	33 (17)	18 (19)	0.7	103 (38)	48 (36)	0.6
Asthma	33 (17)	22 (23)	0.2	86 (32)	41 (31)	0.8
CKD	25 (13)	52 (54)	<0.0001	44 (16)	76 (56)	<0.0001
Comorbidity count			0.0001			0.009
0–1	98 (51)	30 (31)		98 (37)	33 (24)	
2–3	65 (34)	31 (32)		91 (34)	43 (32)	
4+	30 (16)	35 (37)		79 (30)	59 (44)	
RAAS medications	74 (34)	53 (50)	0.005	121 (42)	71 (50)	0.1
Immunosuppression	24 (11)	14 (13)	0.6	131 (45)	66 (46)	0.8
Neutrophil/lymphocyte ratio	4.2 (2.6–8.4)	4.5 (2.9–8.1)	0.2	7.2 (4.0–13.6)	6.8 (4.0–11.2)	0.9
Baseline sCr (mg/dl)	0.8 (0.7–1.0)	1.0 (0.9–1.2)	<0.0001	0.8 (0.7–1.0)	1.0 (0.8–1.2)	<0.0001

Data are presented as median (IQR) or number (%). BMI, body mass index; CAD, coronary artery disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; RAAS, renin angiotensin aldosterone system; sCr, serum creatinine.

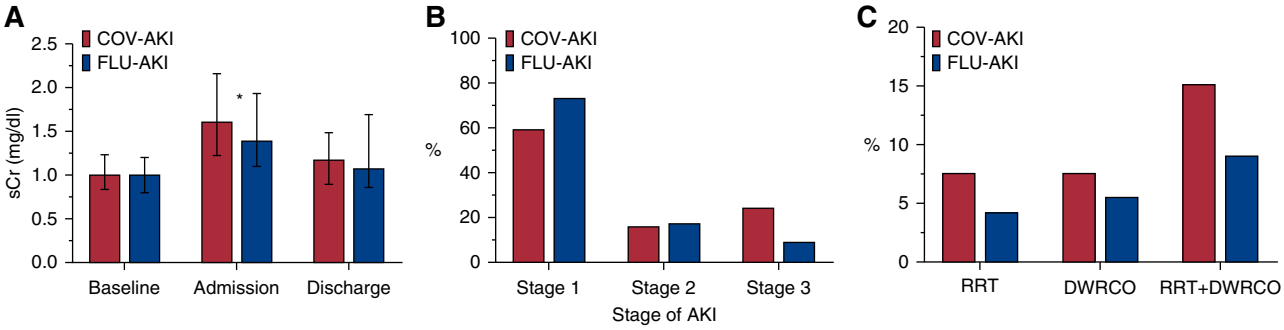

Figure 1. | Characteristics of AKI in coronavirus disease 2019 (COVID-19) and influenza. (A) Baseline, admission, and discharge serum creatinine in patients with AKI. Data are presented at median (interquartile range; IQR). *$P<0.05$. (B) Distribution of AKI stages in patients with COVID-19 or influenza. (C) RRT requirement in patients with AKI. DWRCO, death with rising serum creatinine and oliguria; COV-AKI, AKI in COVID-19; FLU-AKI, AKI in seasonal influenza.

groups. There was also a higher percentage of subjects with stage 3 AKI (25% versus 9%, $P=0.004$) in COV-AKI group versus stage 1 (59% versus 73%, $P=0.004$) and stage 2 AKI (16% versus 18%, $P=0.004$), which were the dominant stages of AKI in the influenza cohort. The proportion of patients requiring RRT (8%), DWRCO (8%), and RRT + DWRCO (15%) was higher in the COV-AKI cohort. The same rates for the FLU-AKI cohort were: RRT (4%), DWRCO (6%), and RRT + DRWCO (9%) although the rate of RRT use between the two groups was not significantly different. The hospitalization characteristics associated with COV-AKI and FLU-AKI are detailed in Table 2. A higher proportion of COV-AKI subjects presented with AKI on admission (72% versus 49%, $P=0.0003$), required mechanical ventilation (24% versus 11%, $P=0.009$) during hospital stay and experienced a higher rate of in-hospital mortality (11% versus 4%, $P=0.02$) in comparison with FLU-AKI. There were no statistically significant differences between the COV-AKI and FLU-AKI groups with regards to ICU admission, vasopressor, and inotrope use, and 30-day mortality.

Table 3 shows the multivariable logistic regression analysis examining the association between virus type and stage 3 AKI. When only considering age and sex, the risk of stage 3 AKI was significantly higher in the COVID-19 cohort in comparison with influenza (OR, 2.63, 95% confidence interval [95% CI], 1.29 to 5.34). After adjusting for the comorbidity count, COVID-19 (OR, 3.46; 95% CI, 1.63 to 7.37), male sex (OR, 2.08; 95% CI, 1.03 to 4.19), and comorbidity count (OR, 1.35; 95% CI, 1.11 to 1.65) were significantly associated with stage 3 AKI. Table 4 shows the multivariable logistic regression analysis examining the association between relevant covariates and AKI, stratified by virus type. When only considering the demographics (age, sex, and race), Black patients were more likely to develop AKI compared with non-Hispanic White patients in both the COVID-19 cohort (OR, 2.54; 95% CI, 1.47 to 4.41) and influenza cohort (OR, 2.37; 95% CI, 1.43 to 3.91); age increase was significantly associated with higher odds of AKI only in the COVID-19 cohort (OR, 1.02; 95% CI, 1.01 to 1.04). After adjusting for comorbidities, age was no longer significant in the COVID-19 cohort, Black race remained significant in the COVID-19 cohort (OR, 2.13; 95% CI, 1.11 to 4.10) but not in the influenza cohort (OR, 1.89; 95% CI 1.05 to 3.39). Patients with CKD were more likely to have AKI compared with patients without CKD in both the COVID-19 cohort (OR, 7.03; 95% CI, 3.44 to 14.38) and influenza cohort (OR, 6.51; 95% CI, 3.81 to 11.11). In the influenza cohort, patients with CHF were more likely to have AKI than those with no history of CHF (OR, 1.9;, 95% CI, 1.08 to 3.37). Patients requiring mechanical ventilation were more likely to develop AKI (OR, 5.85; 95% CI, 2.30 to 15.63) in the COVID-19

Table 2. Hospital characteristics of patients with AKI and COVID-19 or influenza

Clinical Variable	Coronavirus Disease 2019 ($n=106$)	Influenza ($n=143$)	*P* Value
AKI on admission, *n* (%)	76 (72)	70 (49)	0.0003
ICU admission, *n* (%)	60 (57)	65 (46)	0.08
Vasopressor use, *n* (%)	25 (24)	21 (15)	0.07
Inotrope use, *n* (%)	3 (3)	3 (2)	0.7
Mechanical ventilation	25 (24)	16 (11)	0.009
In hospital mortality			0.016
Alive	94 (89)	138 (97)	
Dead	12 (11)	5 (4)	
30-d mortality			0.3
Alive	89 (84)	127 (89)	
Dead	17 (16)	16 (11)	

Data are presented as number (%). ICU, intensive care unit.

Table 3. Independent predictors for stage 3 AKI

Variables	Model 1	Model 2
Virus type		
Influenza (reference)	–	–
COVID-19	2.63[a] (1.29–5.34)	3.46[a] (1.63–7.37)
Sex		
Female (reference)	–	–
Male	1.57 (0.81–3.05)	2.08[b] (1.03–4.19)
Age at admission	1.01 (0.99–1.02)	0.99 (0.97–1.01)
Comorbidity count		1.35[a] (1.11–1.65)

COVID-19, coronavirus disease 2019.
[a]$P<0.01$.
[b]$P<0.05$.
[c]$P<0.001$.

cohort, but not in the influenza cohort (OR, 2.05; 95% CI, 0.76 to 5.58).

Urinalysis results in the patients with COV-AKI and FLU-AKI are shown in Figure 2. Clinically significant hematuria and leukocyturia were defined as >2 red blood cells/high power field and >2 white blood cells/high power field, respectively, whereas clinically significant proteinuria was noted if the urine protein on dipstick was ≥2+. Nephrotic range proteinuria was considered with 3+ proteinuria on urine dipstick (20). In the COV-AKI group, clinically significant hematuria, leukocyturia, and proteinuria were noted in 30%, 39%, and 26% of patients, respectively. Nephrotic range proteinuria was observed in 6% of patients. The FLU-AKI group had similar findings with clinically significant hematuria, leukocyturia, and proteinuria noted in 35%, 35%, and 20% of patients. However, nephrotic range proteinuria was noted in only 3% of patients. *P* values were not calculated due to the high number of missing values for urine findings in both COV-AKI and FLU-AKI groups. A logistic regression model was used to assess the association of urine findings with comorbidities and the findings are shown in Table 5. In comparison with influenza, COVID-19 was associated with 2.3-fold higher odds for dipstick proteinuria 2+ or higher in both unadjusted models (OR, 2.31; 95% CI, 1.23 to 4.40) and after adjusting for comorbidities (OR, 2.33; 95% CI, 1.16 to 4.77). CAD was the sole comorbidity that was associated with a lower risk of proteinuria in the adjusted model (OR, 0.37; 95% CI, 0.15 to 0.85). There was no statistically significant association between comorbidities and hematuria and leukocyturia.

Discussion

The clinical manifestations and outcomes of COVID-19 and influenza are often compared, but little is known about how the risk of AKI compares between these two illnesses (12,13). To our knowledge, this is the first study to compare the prevalence and risk factors for AKI in patients who were hospitalized with COVID-19 and seasonal influenza. Although the rates of AKI are similar in the hospitalized COVID-19 (33%) and influenza cohorts (33%), there are key differences in risk factors. The COV-AKI cohort was younger than the FLU-AKI cohort and had a higher proportion of Black patients and individuals residing in a facility before admission. The COV-AKI cohort was more likely to have underlying DM, HTN, CHF, CAD, pre-existing CKD, and a higher comorbidity count (four or more comorbidities) than the COV-NoAKI cohort. The FLU-AKI cohort was predominantly non-Hispanic White patients, and CHF and pre-existing CKD were identified as significant risk factors in comparison with the FLU-NoAKI group. The FLU-AKI group also had a higher comorbidity count (four or more comorbidities) than FLU-NoAKI. The proportion of individuals with severe AKI, need for mechanical ventilation, and in-hospital mortality were all significantly higher in COV-AKI in comparison with FLU-AKI. The need for mechanical ventilation was associated with higher likelihood of developing COV-AKI in contrast to FLU-AKI. In addition, pre-existing CKD and Black race were two consistent risk factors that were associated with higher odds for AKI in both diseases. Black race was a significant risk factor for COV-AKI, independent of comorbidities.

Black participants have a higher risk of AKI independent of diabetes, hypertension, and CAD, compared with non-Hispanic White participants, which is consistent with our data demonstrating the two-fold higher risk of COV-AKI and FLU-AKI in Black patients in this study. These study findings are consistent with prior studies that demonstrate Black participants with COVID-19 are more likely to have AKI as a complication compared with non-Hispanic White participants (21). Evidence suggests social risk factors such as low income and lack of access to care could explain some of this disparity (22). Recently published studies have reported that Black patients are more likely to be tested for COVID-19 in the emergency department or inpatient settings, and are more likely to be admitted to the hospital compared with non-Hispanic White patients (23–25). This is thought to reflect the lack of access to care and delay in seeking care due to a lack of trust in the system, which results in more advanced disease at the time of presentation (23).

A recently published study by Xie *et al.* (36) reported a higher overall rate of AKI (37% versus 29%), stage 3 AKI (11% versus 3%), and RRT use (5% versus 0.9%) in COVID-19 in comparison with influenza. Although our study reports a similar higher rate of stage 3 AKI (25% versus 9%) in COVID-19, the overall rates of AKI and RRT use were not significantly different between the COVID-19 and

Table 4. Independent predictors for AKI in patients with coronavirus disease 2019 versus influenza

Variables	Coronavirus Disease 2019			Influenza		
	Model 1 Odds Ratio (95% Confidence Interval)	Model 2 Odds Ratio (95% Confidence Interval)	Model 3 Odds Ratio (95% Confidence Interval)	Model 1 Odds Ratio (95% Confidence Interval)	Model 2 Odds Ratio (95% Confidence Interval)	Model 3 Odds Ratio (95% Confidence Interval)
Sex						
Female (reference)	–	–		–	–	
Male	1.42 (0.88 to 2.31)	1.62 (0.91 to 2.89)	1.49 (0.81 to 2.76)	1.42 (0.93 to 2.16)	1.43 (0.87 to 2.33)	1.37 (0.83 to 2.25)
Age at hospital admission	1.02[a] (1.01 to 1.04)	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.02)	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.02)	1.01 (0.99 to 1.02)
Race/ethnicity						
NHW (reference)	–	–	–	–	–	–
B	2.54[a] (1.47 to 4.41)	2.13[b] (1.11 to 4.10)	3.03[a] (1.52 to 6.27)	2.37[a] (1.43 to 3.91)	1.89 (1.05 to 3.39)	1.95[b] (1.07 to 3.54)
Hispanic/ Other	1.21 (0.51 to 2.86)	0.84 (0.28 to 2.53)	0.84 (0.26 to 2.52)	1.29 (0.43 to 3.91)	1.49 (0.44 to 5.03)	1.44 (0.39 to 4.77)
Diabetes						
No (reference)	–	–	–	–	–	–
Yes		1.53 (0.82 to 2.84)	1.39 (0.71 to 2.70)		1.01 (0.61 to 1.68)	0.97 (0.58 to 1.61)
Hypertension						
No (reference)	–	–	–	–	–	–
Yes		1.11 (0.59 to 2.08)	1.26 (0.64 to 2.46)		0.70 (0.40 to 1.21)	0.69 (0.39 to 1.19)
CHF						
No (reference)	–	–	–	–	–	–
Yes		1.68 (0.79 to 3.59)	1.63 (0.73 to 3.61)		1.91[b] (1.08 to 3.37)	1.84[b] (1.04 to 3.29)
CAD						
No (reference)	–	–	–	–	–	–
Yes		0.76 (0.33 to 1.74)	0.82 (0.33 to 1.97)		0.63 (0.34 to 1.14)	0.63 (0.34 to 1.13)
CKD						
No (reference)	–	–	–	–	–	–
Yes		7.03[c] (3.44 to 14.38)	7.84[c] (3.69 to 17.52)		6.51[c] (3.81 to 11.11)	6.66[c] (3.92 to 11.58)
Mechanical ventilation						
No (reference)	–	–	–	–	–	–
Yes			5.85[c] (2.30 to 15.63)			2.05 (0.76 to 5.58)
ICU transfer						
No (reference)	–	–	–	–	–	–
Yes			1.56 (0.80 to 3.04)			1.36 (0.81 to 2.27)

NHW, non-Hispanic White; B, Black; CHF, congestive heart failure; CAD, coronary heart disease; CKD, chronic kidney disease.
[a]$P<0.01$.
[b]$P<0.05$.
[c]$P<0.001$.

influenza groups in our study. This difference can likely be explained by the higher severity of the influenza season (2017–2018), which was evaluated in our study in contrast to the study by Xie *et al.*, where the influenza season from January 2017 to December 2019 was used for comparison. This study by Xie *et al.* also describes CKD as a risk factor for death. The study did not specifically evaluate and describe risk factors for AKI because the primary focus was to describe the clinical presentations in the two diseases and risk of death and resource utilization. We found a higher rate of mechanical ventilation, vasopressor use, in hospital

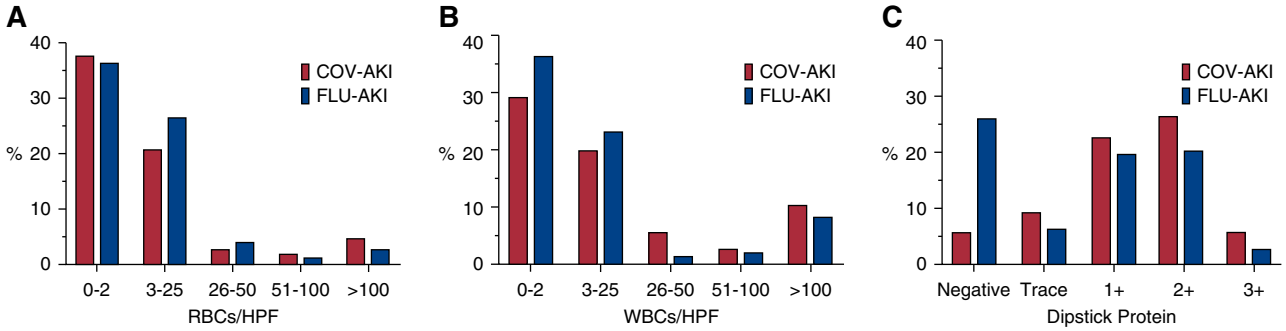

Figure 2. | **Urinalysis findings in patients with AKI in the setting of COVID-19 or influenza.** Distribution of (A) RBCs/HPF, (B) WBCs/HPF, and (C) dipstick proteinuria. RBCs, red blood cells; WBCs, white blood cells; HPF, high power field.

mortality, and LOS in the hospitalized COVID-19 cohort (with and without AKI) similar to the findings reported by Xie *et al.*

In a review of the previously published studies evaluating AKI in COVID-19, our study is comparable in terms of previously reported rates of AKI in New York state (37%–46%) (2,4), Rochester, MN (55%) (26), and New Orleans, Louisiana (28%) (20). These hospital systems were strained early in the COVID-19 pandemic and the numbers of patients with AKI in these studies was much higher than this study (161, Mohamed *et al.*; 179, Nimkar *et al.*; 1993, Hirsch *et al.*; and 1406, Chan *et al.*) The risk factor profile for AKI in patients with COVID-19 in this study is consistent with these earlier reports. Black race, hypertension, and DM

Table 5. Independent clinical predictors of proteinuria, hematuria, and pyuria in coronavirus disease 2019 versus influenza

Variables	Dipstick Proteinuria		RBCs/HPF		WBCs/HPF	
	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Virus type						
Influenza (reference)	–	–	–	–	–	
COVID-19	2.31[a] (1.23 to 4.40)	2.33[a] (1.16 to 4.77)	0.94 (0.50 to 1.75)	1.27 (0.64 to 2.54)	1.32 (0.71 to 2.46)	1.78 (0.90 to 3.60)
Diabetes						
No (reference)	–	–	–	–	–	–
Yes		1.09 (0.53 to 2.20)		0.55 (0.27 to 1.08)		0.52 (0.26 to 1.04)
Hypertension						
No (reference)	–	–	–	–	–	–
Yes		1.87 (0.85 to 4.26)		1.54 (0.73 to 3.29)		1.07 (0.51 to 2.26)
CHF						
No (reference)	–	–	–	–	–	–
Yes		1.04 (0.48 to 2.29)		0.82 (0.38 to 1.75)		1.55 (0.74 to 3.30)
CAD						
No (reference)	–	–	–	–	–	–
Yes		0.37[a] (0.15 to 0.85)		0.84 (0.37 to 1.89)		1.36 (0.62 to 3.06)
CKD						
No (reference)	–	–	–	–	–	–
Yes		1.00 (0.48 to 2.06)		0.86 (0.42 to 1.75)		0.79 (0.39 to 1.58)

CHF, congestive heart failure; CAD, coronary heart disease; CKD, chronic kidney disease.
[a]$P<0.05$; Dipstick proteinuria (>2+), RBCs/HPF: >2, WBCs/HPF: >2.

have also been identified as risk factors for AKI across these studies (2). Our findings support the important association of pre-existing CKD with a higher likelihood of AKI in patients with COVID-19, as reported by Chan *et al.* (4). In the Louisiana study, the median BMI in the AKI group was 34 (IQR, 16–67) kg/m^2 whereas the median BMI in our COV-AKI study population was 28.6 kg/m^2 and not significantly different between the COV-AKI and COV-NoAKI groups. High local prevalence of morbid obesity may thus confer an additional and important risk factor for an increased incidence and severity of AKI during community spread of COVID-19. This may explain the higher rate of RRT requirement in Louisiana (55%). In contrast, the RRT rate in our study was 15%, which is consistent with the observed RRT rates in New York state and Minnesota (2,26). The rate of stage 3 AKI reported in these studies ranged from 21% to 66%, whereas the in-hospital mortality ranged from 35% to 58%. The proportion of stage 3 AKI (25%) and in-hospital mortality (11%) was significantly lower in our study. Disease severity on presentation and the ensuing hospital course, including need for critical care support, may underlie this observed difference in the rates of stage 3 AKI and in-hospital mortality. Because the first wave of COVID-19 in our region was delayed relative to New York and Louisiana, health system readiness and implementation of emerging treatment paradigms (*e.g.*, early proning, less mechanical ventilation, remdesivir) could further explain the lower mortality in our COV-AKI cohort.

AKI in patients who were hospitalized with influenza has been well documented in various studies, on the basis of the clinical experience during the pandemic of 2009 (16,18,27). Although some of these studies focused on AKI in patients who were critically ill (27), several studies assessed AKI in all patients who were hospitalized with influenza (16,18). The reported incidence of AKI in H1N1 influenza varied between 34% and 53%, with in-hospital mortality of approximately 36% and RRT rates of 16–36% for AKI (16,18). Risk factors for AKI in these studies included pregnancy, immunosuppression, DM, COPD, and CKD (16,18,28). In this study, CHF and CKD were associated with a higher risk of AKI in the influenza cohort. Although we report a similar incidence of AKI, the in-hospital mortality (4%) and RRT (9%) rates noted in the FLU-AKI cohort were significantly lower. The prevalent strain during the 2017–2018 influenza season was H3N2 in contrast to the pandemic H1N1 strain of 2009, which was associated with a higher severity of disease. Differences in pathogenicity of the two strains, efficacy of vaccination against the 2017–2018 H3N2 strain, and the possible early initiation of outpatient antiviral therapy could have limited the overall disease severity, and reduced the burden of AKI in the influenza cohort in our study.

Despite a younger median age, the COV-AKI cohort had more comorbidities relative to the FLU-AKI group, indicating that comorbidities may outweigh the benefits of younger age. The severity of AKI was higher in COVID-19, which may indicate a higher overall severity of disease, and can explain the higher in-hospital mortality rate (11% for COV-AKI versus 4% for FLU-AKI). There was no well-established, highly effective treatment for COVID-19 at the time these patients were hospitalized for COVID-19 and supportive medical management was the mainstay of treatment. Remdesivir has been included in treatment protocols in patients who were hospitalized with COVID-19 and has been shown to shorten the recovery period in these patients from 15 to 11 days (29). However, its effect on limiting the severity of disease is not well known. In contrast, the widespread availability of antiviral drugs for the treatment of influenza and early initiation of therapy (which can be done as an outpatient [30]) could have limited the rate of hospitalization and overall severity of disease and associated AKI. Interestingly, in our study, despite a higher rate of stage 3 AKI in COV-AKI, the rate of RRT use or DWRCO was not significantly different between the COV-AKI and FLU-AKI subsets. Hospital systems have been challenged to provide RRT for patients with COV-AKI in a timely and efficient manner (31). With similar rates of RRT noted in the two groups, it is possible the need for RRT resources may substantially increase during the influenza season, assuming a similar rate of hospital admissions, influenza severity, and incidence of AKI, as found in this study.

The pathophysiologic mechanisms of AKI between the two diseases are similar with AKI attributable to hemodynamic insults, myoglobin-induced kidney injury in rhabdomyolysis, and thrombotic microangiopathy (32–34). Hematuria, leukocyturia, and proteinuria are commonly present in patients with AKI in both influenza and COVID-19. The urinalysis findings were similar in the two cohorts in this study, although a higher proportion of patients had nephrotic range proteinuria in COV-AKI (6% versus 3%). COV-AKI is an independent risk factor for development of proteinuria, independent of other comorbidities including diabetes and hypertension. This may be explained in part by glomerular involvement by the severe acute respiratory syndrome coronavirus 2 virus described in recent reports of collapsing glomerulopathy noted in patients with COV-AKI (20). Minimal change disease and membranous nephropathy secondary to COVID-19 have also been reported (35).

The limitations of this study include the retrospective, single-center nature, which may not allow for generalization to the different regions that have seen differential trends of COVID-19 patients and resulting AKI. This study was not designed to assess the effect of available treatment strategies for COVID-19 and influenza on the occurrence of AKI. We were also unable to report and comment on the association of laboratory markers (IL-6, C-reactive protein, and lactate dehydrogenase) with occurrence and severity of COV-AKI due to variability in the local use of these markers in patients with COVID-19. Nephrology consultation was obtained in only a fraction of patients with AKI in both cohorts, so we are limited in our description of the etiology of AKI in both subsets of patients. Strengths of this study include a direct comparison of the characteristics of AKI in COVID-19 and the last severe influenza season (2017–2018). To the best of our knowledge, this is the first study that reports on the differential aspects of AKI in the two diseases. We also analyzed the patterns of RRT use and mechanical ventilation to understand the differences in resource utilization between COVID-19 and severe seasonal influenza.

In conclusion, AKI occurs frequently in patients who were hospitalized with COVID-19 or seasonal influenza. The risk of stage 3 AKI is significantly higher in COVID-19 in

comparison with seasonal influenza. Pre-existing CKD and Black race confer a higher risk for AKI in both illnesses. The need for mechanical ventilation is associated with a disproportionately higher risk for development of COV-AKI. Understanding the patterns of AKI and need for RRT in these two diseases may help inform and advance our knowledge of the renal effect of COVID-19 and influenza.

Disclosures

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Author Contributions

B. Bhasin and K.R. Regner conceptualized the study; B. Bhasin, K.R. Regner, D. Sturgill, and V. Veitla were responsible for data curation; A.Z. Dawson and Z. Garacci were responsible for the formal analysis and methodology; K. R. Regner provided supervision; B. Bhasin, M.N. Ozieh, and K.R. Regner wrote the original draft and revised the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0007322020/-/DCSupplemental.

Supplemental Table 1. ICD-10-CM codes for EHR query.

Supplemental Table 2. Baseline characteristics of the study cohorts.

Supplemental Table 3. Hospital characteristics of the study cohorts.

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Supplementary Table 1. Baseline characteristics of the study cohorts.

Clinical variable	COVID-19 (n=325)	Influenza (n=433)	*P-value*
Age at admission (years)	64 (50-77)	72 (60-84)	<0.0001
Female	158 (48.6)	261 (60.3)	0.001
Race			<0.001
-African American	167 (51.4)	104 (24.0)	
-non-Hispanic white	114 (35.1)	313 (72.3)	
-Hispanic/Other	44 (13.5)	16 (3.7)	
Primary payor			<0.0001
-Medicare	186 (57.2)	331 (76.4)	
-Medicaid	51 (15.7)	49 (11.3)	
-Managed care	66 (20.3)	46 (10.6)	
-Other			
BMI, kg/m^2	30.5 (25.4-36.1)	28.1 (24.0-33.9)	0.007
Residence on admission			<0.001
-Home	251 (77.2)	381 (88.0)	
-Other	74 (22.8)	52 (12.0)	
Diabetes mellitus	127 (43.9)	143 (35.6)	0.03
Hypertension	156 (54.0)	258 (64.2)	0.007
Heart failure	69 (23.9)	112 (27.9)	0.2
CAD	57 (19.7)	117 (29.1)	0.005
PVD	22 (7.6)	45 (11.2)	0.1
COPD	51 (17.7)	151 (37.6)	<0.0001
Asthma	55 (19.0)	127 (31.6)	0.0002
CKD	67 (23.1)	100 (24.9)	0.6
Comorbidity count			0.002
-0-1	128 (44.3)	132 (32.8)	
-2-3	96 (33.2)	136 (33.8)	
-4+	65 (22.5)	134 (33.3)	
RAAS medications	127 (39.1)	192 (44.3)	0.1
Immunosuppression	38 (11.7)	197 (45.5)	<0.0001
Neutrophil/Lymphocyte ratio, median (IQR)	4.3 (2.7 - 8.1)	7.0 (4.0 - 13.0)	<0.0001

Data are presented as median (IQR) or number (%). BMI, body mass index. CAD, coronary artery disease. PVD, peripheral vascular disease. COPD, chronic obstructive pulmonary disease. CKD, chronic kidney disease. RAAS, renin angiotensin aldosterone system.

Supplementary Table 2. Hospital characteristics of the study cohort

Clinical variable	COVID-19 (n=325)	Influenza (n=433)	*P-value*
Nephrology consult	22 (6.8)	14 (3.2)	0.02
ICU admission	141 (43.4)	165 (38.1)	0.1
Vasopressor use	46 (14.2)	41 (9.6)	0.045
Inotrope used	4 (1.2)	3 (0.7)	0.5
Mechanical ventilation	42 (12.9)	28 (6.5)	0.002
In hospital mortality	17 (5.2)	7 (1.6)	0.005
30-day mortality	39 (12.0)	26 (6.0)	0.004
LOS (days)	6.0 (3.0 - 12.0)	4.0 (2.0 - 6.0)	<0.0001

Data are presented as median (IQR) or number (%). ICU, intensive care unit. LOS, length of stay.

Supplementary Table 3.

Influenza codes

J10.00, J10.0, J09.X9, J11.8, J09.X2, J11, J11.0, J11.1, J09, J09.X, J09.X1, J10.1, J10, J11.2, J10.2, J11.81, J11.89, J10.08, J11.00

Cannot have: B97.89, Z03.818

COVD-19 codes

COVID-19 Codes: U07.1, B34.2, B97.29

Cannot have: B97.89, Z03.818